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Abstract for SF298

The purpose of this research is to develop a non-invasive predictor of malignancy in breast tumours through the design and preliminary validation of a new form of magnetic resonance imaging (MRI). The hypothesis is that the spatial distribution of microvasculature around a solid breast lesion is specific for malignancy and can be reliably measured at high resolution by a completely non-invasive, non-contrast-enhanced MRI method. This hypothesis will be tested by achieving the following technical objectives:

1) Design/building/testing of ultra-high-strength gradient coils for human breast imaging at 4T.
2) Design/implementation/testing of MR pulse sequences for selective mapping of microvascular parameters.
3) Evaluation of the correlation of MR-derived microvascular parameters with true microvessel density in a mouse model of human breast cancer.

In order to test this model in animals, a new, extremely high strength gradient coil was required. A mouse-sized gradient coil has been designed with gradient strengths exceeding 2000mT/m, approximately 50 to 100 times stronger than typically found on clinical MRI systems. An MR pulse sequence that allows non-contrast-enhanced imaging through the use of diffusion weighting has been implemented and is currently being tested on our 4T MRI system. A computer program has been written that allows automated analysis of the images.

The significance of this research is that, with relatively low-cost hardware and software modifications to whole-body MR imaging equipment, it should be possible to detect, diagnose, and provide much improved prognosis of lesions suspected to be breast cancer.

FOREWORD

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Date

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Introduction

X-ray mammography is currently the clinically accepted modality for breast cancer screening. Mammography, however, is particularly unreliable and recent trials have shown that 70-80% of mammographically indeterminate lesions that progress to surgical biopsy are benign.[1-4] Development of an accurate, non-invasive imaging test with low false negative rates would allow reduction of the two step process of surgical biopsy followed by surgical lesion removal to a single step, as well as providing a tool for guiding treatment decisions. It may be possible to achieve this through the development of a non-invasive technique that measures microvessel density. Tumour progression is known to be dependent on the ability to stimulate the growth of new blood vessels that supply nutrients and oxygen to the expanding tumour. Based on recent studies that indicate that the onset of angiogenesis can occur before a tumour reaches its maximum diffusion-limited growth potential (1-2 mm diameter) and may occur well before the switch to a malignant phenotype,[5-15] it has been hypothesized that the characteristic new vessel growth associated with tumour angiogenesis should allow differentiation between malignant and benign breast lesions.[16-21] The purpose of this research is to develop a non-invasive predictor of malignancy through the design and preliminary validation of a new form of magnetic resonance imaging (MRI) called the IntraVoxel Incoherent Motion (IVIM) method which utilises high main magnetic field strength and ultra-strong magnetic field gradients. This technology will permit completely non-invasive, quantitative characterization of tumour microvasculature at high spatial resolution over the entire breast.

Body

Hardware Development

An high strength gradient coil has been designed. Because we plan to test our hypothesis in a mouse model, the gradient coil was constructed with an inner diameter of 5cm which is ideal for mice. Gradient strengths achieved with this coil exceeded 2000mT/m, which is 50 to 100 times stronger than typical clinical MRI systems. It was found that wire density and power dissipation considerations required that the coil be constructed in a multilayer configuration. Details regarding the design and construction of the coil are given in the abstract in Appendix I.

Pulse Sequence Development

The IVIM pulse sequence has been designed based on a standard diffusion weighted imaging sequence. The sequence consists of a spin echo planar imaging sequence with the addition of strong magnetic field gradients that cause the contrast in the images to be weighted based on the diffusion of water in the microvascular and extra-vascular compartments. We have incorporated a navigator echo in the pulse sequence. This echo allows post-acquisition correction of the images for small scale motion of the object being imaged. The sequence has been tested on a phantom that is a spherical container (13cm diameter) filled with water and metabolites normally found in the human brain. Sample images are shown in Appendix II showing the expected decrease in signal intensity with increasing b-values. The sequence is currently being tested to determine the effects of eddy currents and large scale motion on the images. Bipolar diffusion gradients and respiratory gating are being examined as a means of reducing image artifacts due to eddy currents and motion of the animal.

A computer program has been written in an interactive windows environment that allows analysis of the diffusion weighted images obtained with the IVIM pulse sequence. Presently, the program allows calculation of the diffusion coefficients of selected regions

of interest within the images. The program has been tested and validated by using two sets of simulated images as input. This data was simulated with four b-values ranging from 0 to 1985 s/mm^2 and diffusion coefficients equal to 2.2×10^{-3} mm^2/s and 0.5×10^{-3} mm^2/s. Values of the diffusion coefficients and chi squared deviations determined by the computer program were $2.21 \pm 0.06 \times 10^{-3}$ mm^2/s and $0.50 \pm 0.08 \times 10^{-3}$ mm^2/s.

The pulse sequence and computer program will be further tested and validated using phantoms containing substances with known diffusion coefficients as well as by imaging the human brain in areas where diffusion coefficients are well documented.[22] Efforts are underway to include multi-step phase contrast and Fourier velocity spectrum data processing capabilities to the computer program.

Validation of Microvascular Imaging

This portion of the study was projected to begin in month 18 (December 1999). Preliminary investigation of animal models of human breast cancer have begun and contacts have been made with animal suppliers. We expected this portion of the study to begin at the scheduled time.

Key Research Accomplishments

- Design of a mouse-sized gradient coil with gradient strengths that exceed 2000mT/m. (Approximately 50 to 100 times higher than typical clinical MRI systems.)
- Implementation of a fast MR pulse sequence that will allow acquisition of diffusion weighted images. Initial tests of the sequence have been performed.
- Design and coding of a computer program that will allow automated analysis of the diffusion weighted images for the calculation of the diffusion coefficients.

Reportable Outcomes

An oral presentation was given at the International Society of Magnetic Resonance in Medicine Seventh Scientific Meeting and Exhibition. The abstract (given in Appendix I) for the meeting was published:
Chronik BA, Alejski A, Rutt BK. A 2000mT/m Multilayer Gradient Coil for Mouse Imaging. *Proc ISMRM* 7:469 (1999).

A post-doctoral fellowship to perform the research supported by this grant was awarded to Dr. Paula Gareau by the Department of Defense Breast Cancer Research Program of the United States Army Medical Research and Materiel Command. Grant Number BC980729.

Conclusions

We have designed a mouse-sized gradient coil with gradient strengths approximately 50 to 100 times higher than typical clinical MRI systems. Based on wire density and power dissipation considerations, we have concluded that small coils with high gradient strengths, such as those required for high resolution IVIM imaging, require multilayer configurations. The design for the mouse-sized coil constructed here should be scalable to a breast-sized coil. Such a coil will allow imaging of the human breast at resolutions that until now have been unattainable, thus allowing visualisation of very small lesions within the breast.

An MR pulse sequence has been implemented on our 4T MRI system that will allow us to acquire IVIM images. Further testing of this sequence is required before conclusions can be drawn regarding its use in the diagnosis of breast lesions.

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Appendix I

PROCEEDINGS

of the

International Society for Magnetic Resonance in Medicine

SEVENTH SCIENTIFIC
MEETING AND EXHIBITION

Philadelphia, Pennsylvania, USA
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Volume 1

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A 2000mT/m Multilayer Gradient Coil for Mouse Imaging

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INTRODUCTION:

Application of advanced, high resolution, high-speed imaging methods in small animals requires the use of extremely high gradient strengths. Here, we discuss the theory and practical issues involved in achieving strengths exceeding 2000mT/m for mouse-sized (inner diameter 5cm) gradient coils. A primary conclusion is that wire density and power dissipation considerations require that such coils be constructed in multilayer configurations.

DESIGN AND FABRICATION:

The scaling laws for changing the dimensions of a single layer wire pattern in the cases of fixed number of wires (N) or a fixed maximum wire density (σ_w) can be shown to be:

for N fixed:

$$\eta \propto a^{-2} \qquad L \propto a \qquad \sigma_w \propto a^{-1} \qquad \Delta T \propto a^{-3}$$

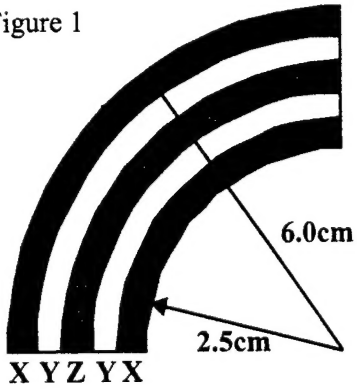
for σ_w fixed:

$$\eta \propto a^{-1} \qquad L \propto a^{3} \qquad N \propto a \qquad \Delta T \propto a$$

where η is the gradient efficiency (gradient produced per unit current), L is the inductance, ΔT the temperature change within the coil, and 'a' is the radius. These expressions show that a typical whole body coil design of radius 30cm, producing 20mT/m (I=200A) with L=1200μH could simply be scaled down (at constant N) to a radius of 3cm and produce 2000mT/m with L=120μH; however, the wire density would increase ten times and the temperature by one thousand times. On the other hand, scaling at constant σ_w would not result in the required gradient strength. In either scenario, single layer approaches are impractical and multilayer designs must be investigated.

We have developed methods of fabricating wire patterns at maximum winding densities of 8-10 wires per cm with rectangular cross section wire (0.8x3.5mm) capable of carrying 200A. Based upon our experience, a layer thickness of 7mm is required to wind this rectangular wire "on end" as well as making connections and return paths. The inner diameter of the finished coil was set at 5cm, which made the winding radius of the first layer 2.775cm and the radii for each successive layer incrementing by 7mm. The design for each layer was obtained using constrained current minimum inductance methods[1] and each produces a region of 1% uniformity over a 15mm diameter spherical volume. Because of the inherently high efficiencies of longitudinal designs from this method, the GZ axis (η=11mT/m/A, L=120μH) could be constructed on one layer with a winding density of 10 wires/cm at a radius of 4.175cm; therefore, only five layers were required for the entire coil and all possible combinations of grouping the four transverse layers into GX and GY coil axes were modeled.

Figure 1



The results of three representative layer orderings are summarized in table 1. Interleaving the GX and GY axis layers is clearly necessary to obtain balanced axes. The optimal five layer configuration for this application was chosen to be the XYZYX ordering as depicted in figure 1. Although several kW of power per axis may be dissipated during extreme applications, it is our experience that this can be handled with a forced water cooling system.

Table 1: Results for Layer Orderings

Ordering		η [mT/m/A]	L [μH]	R [mΩ]
XXZYY	GX	15.0	60	159
	GY	8.1	259	458
XYZXY	GX	12.7	84	261
	GY	10.4	141	358
XYZYX	GX	12.2	121	345
	GY	10.9	114	307

DISCUSSION:

The challenge in designing small, high strength gradient coils is rooted in the fact that multilayer axes are required; therefore, interleaving strategies must be investigated and the problem of designing the complete coil cannot be broken down one axis at a time. The problems of power deposition in single axes of very small coil designs has been discussed before[2]; the novelty in our work is the demonstration of this complete three axis multilayer design compatible with clinical gradient amplifiers and we expect that this will be an important tool in many future mouse and specimen experiments.

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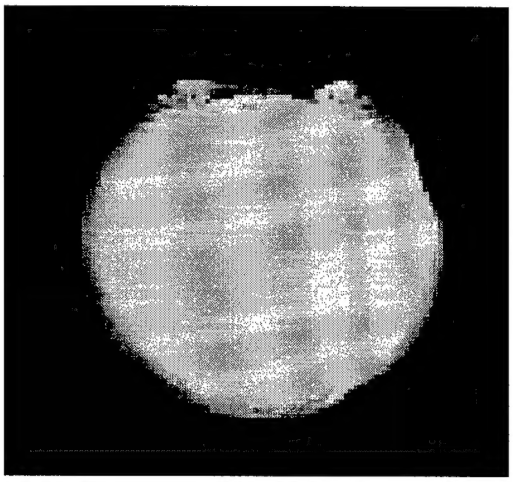
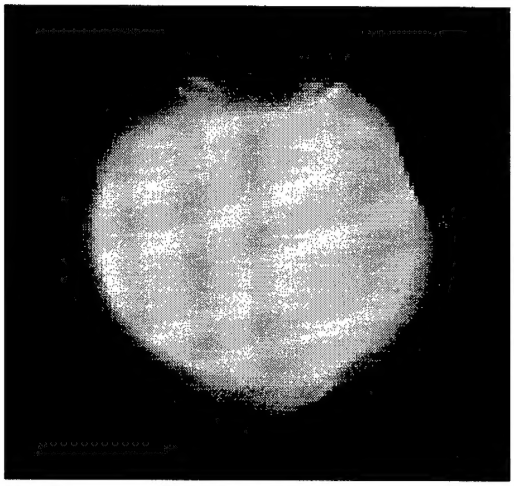
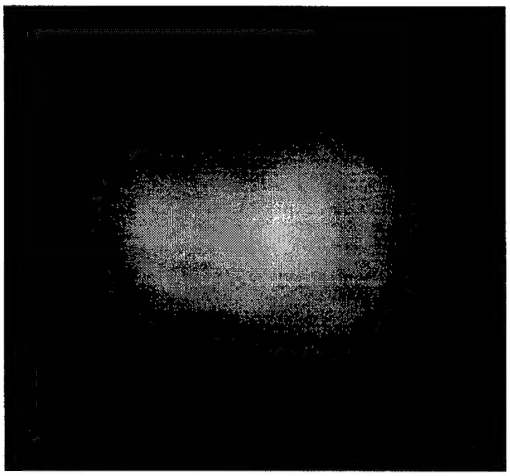
Appendix II



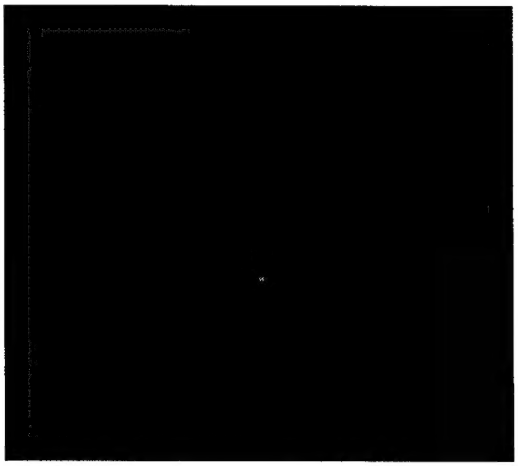
$b = 0.0\ s/mm^2$



$b = 68\ s/mm^2$



$b = 311\ s/mm^2$



$b = 610\ s/mm^2$

Diffusion weighted images of a spherical phantom (13cm diameter) filled with water and metabolites normally found in the human brain. The images show decreasing signal intensity with increasing b-values, as expected.